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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/120,044	07/21/98	MINETTI	C 1758-4036US2

EXAMINER	
DEVI, S	
ART UNIT	PAPER NUMBER
1645	10

HM12/0925

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DATE MAILED: 09/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

*U.S. GPO: 2000-473-000/44602

1- File Copy

Office Action Summary

Application No.	Applicant(s)
09/120,044	Minetti et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 13, 2001*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *35-64* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *43-51* is/are allowed.

6) ☒ Claim(s) *35-38, 40, 41, and 52-64* is/are rejected.

7) ☒ Claim(s) *39 and 42* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 07/13/2001 (paper no. 29) in response to the non-final rejection mailed 04/10/01 (paper no. 28).

Status of Claims

2) Claims 1-15, 22-26 and 31-34 have been canceled via the amendment filed 07/13/2001.

New claims 35-64 have been added via the amendment filed 07/13/2001.

Claims 35-64 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Moot

5) The objection to claims 3, 8 and 33 made in paragraph 11 of the Office Action mailed 04/10/01 (paper no. 28) is moot in light of Applicants' cancellation of the claims.

Rejection(s) Moot

6) The rejection to claims 1-7, 22-26 and 31-34 made in paragraph 8 of the Office Action mailed 04/10/01 (paper no. 28) under 35 U.S.C. § 112, first paragraph, as being non-enabled, is moot in light of Applicants' cancellation of the claims.

7) The rejection to claims 1-7, 22-26 and 31-34 made in paragraph 7 of the Office Action mailed 04/10/01 (paper no. 28) under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

8) The rejection to claims 1-7, 22-26 and 31-34 made in paragraph 9 of the Office Action mailed 04/10/01 (paper no. 28) under 35 U.S.C. § 112, first paragraph, as being non-enabled, is moot in light of Applicants' cancellation of the claims.

9) The rejection to claims 1-7, 22-26 and 31-34 made in paragraph 10 of the Office Action mailed 04/10/01 (paper no. 28) under 35 U.S.C. § 112, first paragraph, as being non-enabled, is moot in light of Applicants' cancellation of the claims.

New Rejection(s)

10) Applicants are asked to note the new rejections made in this Office Action. The Applicants' amendment, i.e., addition of new claims, necessitated the new grounds of rejections presented in this Office Action.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

11) Claims 38-41 and 56-59 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 38 and 56 are vague, indefinite and internally inconsistent in the recitation: "**residue(s)** selected from the group consisting of **positions**" [Emphasis added]. It is unclear how residues can be selected from the group consisting of positions, instead of residues.

(b) Claim 64 is vague in the recitation "polysaccharide .... derived from a bacterium", because it is unclear what is encompassed in this phrase or what do Applicants mean by 'derived'. It is not clear whether this encompasses chemical, non-chemical or genetic "deriving".

(c) Claims 39-41 and 57-59, which depend directly or indirectly, from claim 38 or 56, are also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, because of the vagueness in the base claim as identified above.

Rejection(s) under 35 U.S.C. § 112, First Paragraph

12) Claims 38 and 56 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a modified, refolded pneumolysin mutant having attenuated hemolytic activity, wherein the pneumolysin polypeptide is substituted at the amino acid position 61, 148 **or** 195, does not reasonably provide enablement for a refolded, modified pneumolysin mutant having amino acid substitutions at more than one position selected from the group consisting of position 61, 148 and 195, as recited currently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly

connected, to make and/or use the invention commensurate in scope with these claims.

Instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention includes modifying or attenuating a wild-type pneumolysin polypeptide by random mutation of the nucleic acid molecule. The breadth of the claims encompasses a refolded, modified, hemolytically attenuated, pneumolysin polypeptide obtained by mutation of the nucleic acid molecule encoding a wild type pneumolysin at more than one of the recited positions: 61, 148 and 195. However, a review of the instant disclosure suggests that a modified, attenuated pneumolysin having more than one substitution at positions 61, 148 and 195 is not enabled. Table 5A provides enablement for a modified pneumolysin having a substitution at any one of positions 61, 148 **or** 195, but not for a modified pneumolysin having substitutions at more than one of these positions. There appears to be no evidence within the instant specification enabling a double or triple pneumolysin mutant comprising two or three amino acid substitutions at positions 61, 148 and 195 of SEQ ID NO: 3, which mutant is refolded and has attenuated hemolytic properties. The art reflects that refoldability of a protein and attenuation of the hemolytic activity of a wild-type pneumolysin by random mutations are unpredictable events. The instant specification states that multiple mutations are unpredictable (see lines 8 and 9 on page 27). The specification discloses that even with a substitution at a single amino acid position, let alone combination of substitutions, the refoldability of the resultant single mutant polypeptide is not predictable. For instance, the specification discloses that a single mutation at position 243 of the wild-type pneumolysin, or a combination of substitutions that includes position 243, resulted in insoluble inclusion bodies, and attempted

refolding of the mutant yielded aggregate species (see pages 57 and 58, and Table 5B). Obviously, such an insoluble and non-refolded or non-functional pneumolysin would lack the structural, functional and immunogenic and/or biological integrity, and therefore, is not an ideal vaccine candidate or an ideal protein carrier. There is no evidence that a pneumolysin polypeptide having, for example, amino acid substitutions at positions 61, 148 and 195 would be haemolytically attenuated and correctly refolded such that it would serve as an optimal vaccine or an effective protein carrier.

In view of the recognized unpredictability of obtaining an attenuated, refolded, functional modified pneumolysin by any random mutation(s), Applicants' own evidence showing that refolding and hemolysis-attenuating properties of a single or multiple mutant of pneumolysin are unpredictable events, the quantity of experimentation necessary and the breadth of the claims, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the full scope of the invention as claimed. The breadth of instant claims is not commensurate in scope with the enabling disclosure and/or evidence and therefore, one skilled in the art cannot make and use the invention commensurate in scope with the claims without undue experimentation.

13) Claims 40, 41, 58 and 59 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a modified, attenuated, refolded pneumolysin having a single amino acid substitution wherein the substitution is proline at position 61, lysine at position 148, and isoleucine or valine at position 195, does not reasonably provide enablement for a modified, refolded, attenuated pneumolysin mutant having a single amino acid substitution wherein the substitution is hydroxyproline at position 61, arginine or histidine at position 148, and leucine, glycine or alanine at position 195, as claimed currently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims. No

Instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);

- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to a modified, attenuated and refolded pneumolysin polypeptide meant for use as a vaccine or a protein carrier in a conjugate vaccine. Table 5A shows that a functional attenuated and refolded pneumolysin is obtained when proline is substituted at position 61, lysine at position 148, and isoleucine or valine at position 195. However, there is no evidence within the instant specification showing that a functional, haemolytically attenuated and refolded pneumolysin suitable for use as a vaccine or protein carrier is obtained when hydroxyproline is substituted at position 61, arginine or histidine at position 148, and leucine, glycine or alanine at position 195, as claimed currently. There is no certainty that substitution at positions 61, 148 or 195 with these amino acids would result in a modified, attenuated and refolded pneumolysin. There is no certainty that the resultant modified pneumolysin would retain the functional integrity or biological/immunogenic competence of the native pneumolysin, without rendering it non-functional. See paragraph 10 of the Office Action mailed 04/10/01 for an explanation of the unpredictability factor involved in making any random amino acid substitutions at any one specific position and obtaining a functional or desired modified protein. Undue experimentation would have been required by one of ordinary skill in the art to practice the invention due to the lack of specific evidence, the breadth of the claims, the art-known unpredictability, the quantity of experimentation necessary and the lack of working examples enabling attenuated, refolded and functional pneumolysin mutant species having hydroxyproline substitution at position 61, arginine or histidine substitution at position 148, and leucine, glycine or alanine substitution at position 195.

Rejection(s) under 35 U.S.C. § 102

14) Claim 35 is rejected under 35 U.S.C. § 102(b) as being anticipated by Lock *et al.* (*Microb. Pathogen.* 21: 71-83, 1996 - Applicants' IDS).

It is noted that the instant specification lacks a precise definition for the recitation

"refolded". For the purpose of this rejection, the claim is viewed as encompassing partially refolded, fully refolded, correctly refolded, or incorrectly refolded, modified pneumolysins.

Lock *et al.* teach a modified pneumolysin, Ply8, having substantially reduced haemolytic activities compared to wild type pneumolysin, Ply, as tested by a haemolytic assay. Ply has the amino acid sequence of the instantly recited SEQ ID NO: 3 (see abstract and Figure 3). Ply 8, produced by the host cells, has a single amino acid substitution at position 172 (see abstract; and pages 75 and 80). The modified pneumolysin is in a phosphate buffer, i.e., a pharmaceutically acceptable carrier (see page 81). Lock *et al.* explicitly teach that antibodies "raised against Ply completely neutralize Ply8 haemolytic activity and **vice versa**" (see page 80) (Emphasis added). That antibodies are raised against Ply8, which neutralize native Ply, clearly suggests that Lock's Ply8 is correctly refolded. Lock *et al.* expressly teach that Ply toxoid is a promising candidate for inclusion in the next generation of pneumococcal vaccines (see page 78).

Claim 35 is anticipated by Lock *et al.*

15) Claims 35-37, 52-55 and 62 are rejected under 35 U.S.C. § 102(b) as being anticipated over Hill *et al.* (*Infect. Immun.* 62: 757-758, 1994 - Applicants' IDS).

35-37, 53, 62

It is noted that the instant specification lacks a precise definition for the recitation "refolded". For the purpose of this rejection, the claims are viewed as encompassing partially refolded, fully refolded, correctly refolded, or incorrectly refolded, modified pneumolysins. It is noted that instant claims encompass a modified pneumolysin as recited, having "at least one" amino acid substitution in the region of pneumolysin (SEQ ID NO: 3) comprising amino acid residues 1 to 257. Any single pneumolysin mutant having an amino acid substitution in the region of 1 through 257 of SEQ ID NO: 3 is encompassed in the scope of the claims.

Hill *et al.* teach a randomly mutagenized (i.e., modified) pneumolysin having reduced (i.e., attenuated) hemolytic activity due to an amino acid substitution within the N-terminal region of pneumolysin (see abstract). Modified pneumolysins having a single mutation at position 31, 127 and 156 showed reduced hemolytic activity (see Table 1). The modified pneumolysin is obtained by randomly mutating the pneumolysin gene, expressing the mutated molecule in a host cell and assaying the hemolytic activity of the modified pneumolysin and is contained in PBS, i.e., pharmaceutically acceptable carrier (see page 757). Because the structural

limitation of having at least one amino acid substitution in the region comprising amino acids 1 to 257 has been met by the prior art pneumolysin mutants, the refolding property is viewed as an inherent property of Hill's pneumolysin mutants. One mutant had 98% less hemolytic activity compared to the wild-type pneumolysin (see Table 1; and page 757 and 758).

Claims 35-37, 52-55 and 62 are anticipated by Hill *et al.*

Rejection(s) under 35 U.S.C. § 103

16) Claims 52 and 60-64 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Paton *et al.* (*Infect. Immun.* 59: 2297-2304, 1991 - Applicants' IDS) in view of Hill *et al.* (*Infect. Immun.* 62: 757-758, 1994 - Applicants' IDS) and Krishnamurthy *et al.* (*Infect. Immun.* 22: 727-735, 1978, already of record), or Lee *et al.* (*J. Infect. Dis.* 151: 658-664, 1985, already of record).

It is noted that Applicants use the terms, pneumolysoid and modified pneumolysin, interchangeably in the instant specification (see page 6, lines 8 and 9, for example).

Paton *et al.* teach modified pneumolysins or pneumolysoids or pneumolysin toxoids designated Pd-A and Pd-B. Pd-A carries a single mutation, i.e., a Cys->Gly amino acid substitution at position 428, whereas Pd-B carries a Trp->Phe substitution at position 433 (see abstract and page 2298, left column). The two pneumolysoids show a reduced or attenuated hemolytic activity compared to that of native pneumolysin (see page 2299, right column, first paragraph under 'Results'). The pneumolysoids are produced by site-directed mutagenesis or single amino acid substitutions, which significantly reduce the hemolytic activity (see page 2298). The pneumolysoids are expressed by *E. coli* host cells and are assayed for hemolytic activity (see page 2298, right column, first paragraph). Both Pd-A and Pd-B contained in a pharmaceutically acceptable carrier, such as PBS, are taught (see page 2299, left column). Paton *et al.* teach the conjugation of Pd-B to the pneumococcal serotype 19F polysaccharide; a vaccine comprising the same is also taught (see page 2299, left column). That Paton's Pd-B pneumolysoid (i.e., modified pneumolysin) having an attenuated haemolytic activity served as an effective immunogen, with and without conjugation to a polysaccharide, suggests that the pneumolysoid was correctly refolded.

Paton *et al.* do not teach a modified, attenuated pneumolysin polypeptide having at least one amino acid substitution in the region comprising amino acids 1 to 257 being conjugated to a

polysaccharide that elicits antibodies cross-reactive with a bacterial polysaccharide.

However, Hill *et al.* teach a modified, haemolytically attenuated pneumolysin polypeptide having at least one amino acid substitution in the region comprising amino acids 1 to 257 as explained above.

The cross-reactivity of Paton's pneumococcal serotype 19F capsular polysaccharide with certain heterologous bacterial polysaccharides is a property necessarily present in the 19F polysaccharide as is evident from the state of the art. For instance, Krishnamurthy *et al.* teach that the capsular polysaccharide of serotype 19F pneumococcus is cross-reactive with the capsular polysaccharide of serotype 19A pneumococcus (see abstract). Similarly, Lee *et al.* teach the cross-reactivity and structural similarities between the capsular polysaccharides of serotype 19F pneumococcus and *Klebsiella* K2 (see abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute Paton's pneumolysoid with Hill's modified pneumolysin that carries an attenuating mutation at a position between amino acid residues 1 to 257 to produce the instant invention, with a reasonable expectation of success. The substitution of one pneumolysoid with an alternative, art-available pneumolysoid for the same or similar purpose would have been obvious to a skilled artisan and would have been expected to bring about similar results or effects, absent evidence to the contrary.

Claims 52 and 60-64 are *prima facie* obvious over the prior art of record.

Objection(s)

17) Claims 39 and 42 are free of prior art of record, but are objected to for being dependent from a rejected base claim.

Remarks

18) Independent claims 43-51 are allowed. Claims 39 and 42 stand objected to. Claims 35-38, 40, 41 and 52-64 stand rejected.

19) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE

MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week.

21) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

September 2001

S. DEVI, PH.D.
PRIMARY EXAMINER